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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE DIVISIONAL APPLICATION OF:

William J. Curatolo, et al.

SERIAL NO.: **09/577,059**

: EXAMINER: **R. Dewitty**

FILED: **May 22, 2000**

: ART UNIT: **1616**

FOR: **Controlled-Release Dosage
Forms of Azithromycin**

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT UNDER RULE 114

This is in response to the Office Action dated March 26, 2003 in the above-identified application, the term for response having been extended three (3) months to September 26, 2003 by including the appropriate fee and petition herewith.

This response is submitted together with a Request For Continued Examination (RCE). Withdrawal of the finality of the Office Action is accordingly requested.

Attention is additionally directed to the Information Disclosure Statement also submitted herewith.

A copy of the claims status is presented as the following item, starting on the next sheet.

72. (currently amended) A sustained release dosage form comprising azithromycin which meets the following in vitro criteria:

- (1) $Q_{0.25} \leq 200$ mg,
- (2) $Q_1 \leq 500$ mg,
- (3) $Q_2 \leq 1000$ mg,
- (4) $Q_4 \leq 1500$ mg, and
- (5) $Q_6 \leq 2000$ mg,

when said dosage form is tested in a USP rotating paddle apparatus, said apparatus being described in USP XXIII dissolution test chapter 711, and wherein the apparatus has paddles rotating at 50 rpm and contains 900 mL of pH 6.0 sodium dihydrogen phosphate buffer at 37°C;

and wherein, if said dosage form is a capsule, said buffer is implemented to contain 0.1 mg/mL of trypsin[.]

and wherein said dosage form releases not more than 70% of its contained azithromycin within one half hour following ingestion.

73. (previously presented) A dosage form as defined in claim 72, wherein said azithromycin is embedded in a matrix, which releases said azithromycin by diffusion.

74. (previously presented) A dosage form as defined in claim 73, wherein said matrix remains substantially intact during the period of drug release.

75. (previously presented) A dosage form as defined in claim 73, wherein said azithromycin is embedded in a matrix which releases said azithromycin by eroding.

76. (previously presented) A dosage form as defined in claim 75, wherein said matrix comprises hydroxypropyl methylcellulose.

77. (withdrawn) A dosage form as defined in claim 75, wherein said matrix comprises hydroxypropyl cellulose.

78. (withdrawn) A dosage form as defined in claim 75, wherein said matrix comprises poly(ethylene oxide).

79. (withdrawn) A dosage form as defined in claim 75, wherein said matrix comprises polyacrylic acid.

80. (previously presented) A dosage form as defined in claim 72, comprising a reservoir of azithromycin encased in a membrane which limits the release rate of azithromycin to said GI tract by diffusion.

81. (previously presented) A dosage form as defined in claim 80, in the form of a tablet coated with a membrane.

82. (previously presented) A dosage form as defined in claim 72, in the form of a multiparticulate comprising particles each of which is coated with a membrane which limits the release rate of said azithromycin by diffusion.

83. (previously presented) A dosage form as defined in claim 73, wherein a portion of the outside surface of said matrix is covered with an impermeable coating and the remainder of said outside surface is uncovered.

84. (previously presented) A dosage form as defined in claim 83, substantially in the shape of a cylinder wherein said impermeable coating covers one or both of the opposing flat surfaces thereof.

85. (previously presented) A dosage form as defined in claim 83, substantially in the shape of a cylinder wherein said impermeable coating covers only the radial surface thereof.

86. (previously presented) A dosage form as defined in claim 83, in the form of a tablet, wherein said uncovered area is in the form of an opening through said impermeable coating.

87. (withdrawn) A dosage form as defined in claim 83, in the form of a tablet, wherein said uncovered area is in the form of a passageway which penetrates through the entire device.

88. (withdrawn) A dosage form as defined in claim 83, in the form of a tablet, wherein said uncovered area is in the form of one or more slits through said impermeable coating or in the form of one or more strips removed therefrom.

89. (withdrawn) A dosage form as defined in claim 83, substantially in the form of a cone, wherein the uncovered area an opening for drug transport at or near the apex of the cone.

90. (withdrawn) A dosage form as defined in claim 83, substantially in the shape of a hemisphere, wherein the uncovered area is in the form of an opening for drug transport at or near the center of the flat face of the hemisphere.

91. (withdrawn) A dosage form as defined in claim 83, substantially in the shape of a half-cylinder, wherein the uncovered area is in the form of one or more slits at or near the centerline of the flat face of said half-cylinder.

92. (withdrawn) A dosage form as defined in claim 72 in the form of a coated bi-layer tablet, wherein one layer of said tablet comprises a water-swellaable composition and the second layer of said tablet comprises a dispensible azithromycin composition, said tablet being coated with a water-permeable membrane which is substantially impermeable to azithromycin, and which contains one or more perforations or passageways for exposing the azithromycin-containing composition to the use environment.

93. (previously presented) A dosage form as defined in claim 72 in the form of a coated tablet comprising a water-soluble salt of azithromycin, said tablet having a water-permeable coating which is substantially impermeable to azithromycin and substantially non-porous, said coating containing one or more perforations or passageways, for exposing the interior of the tablet to a use environment.

94. (previously presented) A dosage form as defined in claim 72 in the form of a coated tablet comprising azithromycin, said tablet having a porous coating which permits transport of both water and azithromycin through said porous coating.

95. (previously presented) A dosage form as defined in claim 72 in the form of a coated multiparticulate formulation wherein each particle comprises azithromycin and has a porous coating which permits transport of both water and azithromycin through said porous coating.

96. (previously presented) A delayed release dosage form comprising azithromycin which meets the following in vitro criteria:

in a first dissolution stage, $Q_{0.25} < 10\%$ when said dosage form is inserted in a USP rotating paddle apparatus, said apparatus being described in USP XXIII dissolution test chapter 711, and wherein said apparatus has paddles rotating at 50 rpm and contains 750 mL of 0.1 N HCl at 37°C;

in a second dissolution stage, $Q_{0.5} < Q_{0.25} + 10\%$ when 250 mL of 0.2 M tribasic sodium phosphate buffer is added to said acid immediately following said first stage to implement a buffer having a pH of about 6.8.

97. (previously presented) A dosage form as defined in claim 96, in the form of a tablet.

98. (previously presented) A dosage form as defined in claim 96, comprising a multiparticulate having a diameter between about 0.5 mm and about 3 mm.

99. (previously presented) A dosage form as defined in claim 96, comprising a multiparticulate having a diameter between about 0.1 and about 0.5 mm.

100. (previously presented) A dosage form as defined in claim 97, coated with a membrane comprising a polymer which is substantially insoluble and/or impermeable to azithromycin at the pH of the stomach, and is soluble and/or permeable to azithromycin at the pH of the small intestine and colon.

101. (previously presented) A dosage form as defined in claim 100, wherein said polymer is selected from cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methylcellulose phthalate, and copolymers comprising acrylic acid and at least one acrylic acid ester.

102. (previously presented) A dosage form as defined in claim 98, wherein said multiparticulate is coated with a membrane comprising a polymer that is substantially insoluble and/or impermeable to azithromycin at the pH of the stomach, and is soluble and/or permeable to azithromycin at the pH of the small intestine and colon.

103. (previously presented) A dosage form as defined in claim 102, wherein said polymer is selected from cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methylcellulose phthalate, and copolymers comprising acrylic acid and at least one acrylic acid ester.

104. (previously presented) A dosage form as defined in claim 99, wherein said multiparticulate is coated with a membrane comprising a polymer that is substantially insoluble and/or impermeable to azithromycin at the pH of the stomach, and is soluble and/or permeable to azithromycin at the pH of the small intestine and colon.

105. (previously presented) A dosage form as defined in claim 104, wherein said polymer is selected from cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methylcellulose phthalate, and copolymers comprising acrylic acid and at least one acrylic acid ester.

106. (previously presented) A dosage form as defined in claim 97, wherein said tablet optionally further comprises one or more osmagents, said tablet being surrounded by a semipermeable membrane that is permeable to water and substantially impermeable to said azithromycin and said osmagents.

107. (previously presented) A dosage form as defined in claim 98, said multiparticulate further comprising one or more osmagents, said multiparticulate being surrounded by a semipermeable membrane that is permeable to water and substantially impermeable to azithromycin and osmagents.

108. (previously presented) A dosage form as defined in claim 97, further comprising at least one swellable material, said tablet being surrounded by a semipermeable membrane that is permeable to water and substantially impermeable to azithromycin and said swellable material.

109. (previously presented) A dosage form as defined in claim 98, further comprising at least one swellable material, each multiparticulate particle being surrounded by a semipermeable membrane that is permeable to water and substantially impermeable to azithromycin and said swellable materials.

110. (previously presented) A dosage form as defined in claim 97, comprising:
a core comprising azithromycin and at least one osmagent;
a wall surrounding said tablet comprising a semipermeable membrane which is permeable to water and substantially impermeable to azithromycin and osmagent; and
a pH-sensitive trigger means attached to said semipermeable membrane for triggering the bursting of the tablet, said trigger means triggering at a pH between 3 and 9.

111. (previously presented) A dosage form as defined in claim 98, said multiparticulate further comprising

one or more osmagents, each multiparticulate being surrounded by a wall comprising a semipermeable membrane which is permeable to water and substantially impermeable to azithromycin and osmagent; and
a pH-sensitive trigger means attached to said semipermeable membrane for triggering the bursting of the multiparticulate said trigger means triggering at pH between 3 and 9.

112. (previously presented) An azithromycin dosage form as defined in claim 110, wherein said core further comprises at least one swelling material.

113. (previously presented) An azithromycin dosage form as defined in claim 111, wherein said multiparticulate further each comprise at least one swelling material.

114. (previously presented) A dosage form as defined in claim 97, comprising:
a core comprising azithromycin and at least one osmagent;
a membrane surrounding said tablet core wherein said membrane is fabricated from a microporous hydrophobic support material;
a hydrophobic liquid entrained within said membrane, said hydrophobic liquid being substantially impermeable to water and azithromycin, but being capable of changing to become substantially permeable to water and azithromycin.

115. (previously presented) A dosage form as defined in claim 98, comprising:
a core comprising azithromycin and at least one osmagent;
a membrane surrounding said multiparticulate core wherein said membrane is fabricated from a microporous hydrophobic support material;
a hydrophobic liquid entrained within said membrane, said hydrophobic liquid being substantially impermeable to water and azithromycin, but being capable of changing to become substantially permeable to water and azithromycin.

116. (previously presented) An azithromycin-containing dosage form as defined in claim 97, comprising:
a core comprising azithromycin and at least one swelling material;
a membrane surrounding said tablet core wherein said membrane is fabricated from a microporous hydrophobic support material;
a hydrophobic liquid entrained within said membrane, said hydrophobic liquid being substantially impermeable to water and azithromycin, but being capable of changing to become substantially permeable to water and azithromycin.

117. (previously presented) A dosage form as defined in claim 98, comprising:
a core comprising azithromycin and at least one swelling material;
a membrane surrounding said multiparticulate core wherein said membrane is fabricated from a microporous hydrophobic support material;
a hydrophobic liquid entrained within said membrane, said hydrophobic liquid being substantially impermeable to water and azithromycin, but being capable of changing to become substantially permeable to water and azithromycin.

118. (previously presented) A dosage form as defined in claim 97, comprising:
a core comprising azithromycin and at least one swelling material and/or at least one osmagent;
a membrane surrounding said tablet core wherein said membrane is substantially impermeable to azithromycin and labile to enzymes produced by bacteria which inhabit the colon.

119. (previously presented) A dosage form as defined in claim 98, comprising:
a core comprising azithromycin and at least one swelling material and/or at least one osmagent;
a membrane surrounding said multiparticulate core wherein said membrane is substantially impermeable to azithromycin and labile to enzymes produced by bacteria which inhabit the colon.

120. (previously presented) A dosage form as defined in claim 118, wherein said membrane comprises a polymer comprising at least one ethylenically unsaturated monomer crosslinked by a substituted or unsubstituted divinylazobenzene.

121. (previously presented) A dosage form as defined in claim 119, wherein said membrane comprises a polymer comprising at least one ethylenically unsaturated monomer crosslinked by a substituted or unsubstituted divinylazobenzene.

122. (previously presented) A dosage form as defined in claim 118, wherein said membrane comprises at least one polysaccharide.

123. (previously presented) A dosage form as defined in claim 119, wherein said membrane comprises at least one polysaccharide.

124. (previously presented) A dosage form as defined in claim 96, in the form of a capsule comprising two interpenetrating pieces, a first male piece comprising a water-swellaable material, which swells to effect disengagement of a second female piece upon administration to said mammal.

125. (currently amended) A sustained release dosage form comprising azithromycin for ingestion by a mammal which meets, based on the weight of said mammal, the following in vitro criteria:

- (1) $Q_{0.25} \leq 4$ mg/Kg of mammal weight,
- (2) $Q_1 \leq 10$ mg/Kg of mammal weight,
- (3) $Q_2 \leq 20$ mg/Kg of mammal weight,
- (4) $Q_4 \leq 30$ mg/Kg of mammal weight, and
- (5) $Q_6 \leq 40$ mg/Kg of mammal weight,

when said dosage form is tested in a USP rotating paddle apparatus, said apparatus being described in USP XXIII dissolution test chapter 711, and wherein the apparatus has paddles rotating at 50 rpm and contains 900 mL of pH 6.0 sodium dihydrogen phosphate buffer at 37°C;

and wherein, if said dosage form is a capsule, said buffer is implemented to contain 0.1 mg/mL of trypsin[.].

and wherein said dosage form releases not more than 70% of its contained azithromycin within one half hour following ingestion.

126. (previously presented) A dosage form as defined in claim 125, wherein said azithromycin is embedded in a matrix, which releases said azithromycin by diffusion.

127. (previously presented) A dosage form as defined in claim 126, wherein said matrix remains substantially intact during the period of drug release.

128. (previously presented) A dosage form as defined in claim 126, wherein said azithromycin is embedded in a matrix which releases said azithromycin by eroding.

129. (previously presented) A dosage form as defined in claim 128, wherein said matrix comprises hydroxypropyl methylcellulose.

130. (withdrawn) A dosage form as defined in claim 128, wherein said matrix comprises hydroxypropyl cellulose.

131. (withdrawn) A dosage form as defined in claim 128, wherein said matrix comprises poly(ethylene oxide).

132. (withdrawn) A dosage form as defined in claim 128, wherein said matrix comprises polyacrylic acid.

133. (previously presented) A dosage form as defined in claim 125, comprising a reservoir of azithromycin encased in a membrane which limits the release rate of azithromycin to said GI tract by diffusion.

134. (previously presented) A dosage form as defined in claim 133, in the form of a tablet coated with a membrane.

135. (previously presented) A dosage form as defined in claim 135, in the form of a multiparticulate comprising particles each of which is coated with a membrane which limits the release rate of said azithromycin by diffusion.

136. (previously presented) A dosage form as defined in claim 126, wherein a portion of the outside surface of said matrix is covered with an impermeable coating and the remainder of said outside surface is uncovered.

137. (previously presented) A dosage form as defined in claim 136, substantially in the shape of a cylinder wherein said impermeable coating covers one or both of the opposing flat surfaces thereof.

138. (previously presented) A dosage form as defined in claim 136, substantially in the shape of a cylinder wherein said impermeable coating covers only the radial surface thereof.

139. (previously presented) A dosage form as defined in claim 136, in the form of a tablet, wherein said uncovered area is in the form of an opening through said impermeable coating.

140. (withdrawn) A dosage form as defined in claim 136, in the form of a tablet, wherein said uncovered area is in the form of a passageway which penetrates through the entire device.

141. (withdrawn) A dosage form as defined in claim 136, in the form of a tablet, wherein said uncovered area is in the form of one or more slits through said impermeable coating or in the form of one or more strips removed therefrom.

142. (withdrawn) A dosage form as defined in claim 136, substantially in the form of a cone, wherein the uncovered area is an opening for drug transport at or near the apex of the cone.

143. (withdrawn) A dosage form as defined in claim 136, substantially in the shape of a hemisphere, wherein the uncovered area is in the form of an opening for drug transport at or near the center of the flat face of the hemisphere.

144. (withdrawn) A dosage form as defined in claim 136, substantially in the shape of a half-cylinder, wherein the uncovered area is in the form of one or more slits at or near the centerline of the flat face of said half-cylinder.

145. (withdrawn) A dosage form as defined in claim 125 in the form of a coated bi-layer tablet, wherein one layer of said tablet comprises a water-swellaable composition and the second layer of said tablet comprises a dispensible azithromycin composition, said tablet being coated with a water-permeable membrane which is substantially impermeable to azithromycin, and which contains one or more perforations or passageways for exposing the azithromycin-containing composition to the use environment.

146. (previously presented) A dosage form as defined in claim 125 in the form of a coated tablet comprising a water-soluble salt of azithromycin, said tablet having a water-permeable coating which is substantially impermeable to azithromycin and substantially

non-porous, said coating containing one or more perforations or passageways, for exposing the interior of the tablet to a use environment.

147. (previously presented) A dosage form as defined in claim 125 in the form of a coated tablet comprising azithromycin, said tablet having a porous coating which permits transport of both water and azithromycin through said porous coating.

148. (previously presented) A dosage form as defined in claim 125 in the form of a coated multiparticulate formulation wherein each particle comprises azithromycin and has a porous coating which permits transport of both water and azithromycin through said porous coating.
